MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 15, 2004

PID #: D030547

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SUBJECT: 1-year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
Drug: Nelfinavir Tablets (250 mg and 625 mg) and Oral Powder (Viracept®, Agouron Pharmaceuticals, NDA 20-778, 20-779, and 21-503)

Pediatric Exclusivity Approval Date: September 4, 2003

1 EXECUTIVE SUMMARY

The AERS database was searched for reports of adverse events occurring with the use of nelfinavir in pediatric patients. Overall, AERS contains 3344 cases (raw count) for nelfinavir, including both adult and pediatric cases, and cases with no age reported (null values). Pediatrics reports represent 377 of the total reports.

DDRE was asked to focus on the 1-year period following the approval of pediatric exclusivity, September 4, 2003 to September 4, 2004 (referred to hereafter as the *pediatric exclusivity period*). We used an AERS "cut-off" date of October 4, 2004 to allow time for all reports received by September 4, 2004 to be entered into AERS. A total of 269 cases (raw count) were received in the pediatric exclusivity period, including both adult and pediatric cases, and cases with no age reported. Thirty (raw count) of the 269 cases received in the pediatric exclusivity period reported events in pediatric patients.

We reviewed **27** unique pediatric cases (the other 3 are duplicate reports) reported to the FDA during the pediatric exclusivity period resulting in **3** pediatric reports in patients receiving nelfinavir for the treatment of HIV and an additional **24** reports in infants following transplacental exposure to nelfinavir.

Of the 3 unduplicated reports in pediatric patients receiving nelfinavir, two were literature reports and the third described an attention deficit/hyperactivity disorder in 14 year old male patient. Causality attribution to nelfinavir in the two literature cases describing neuromuscular weakness and obliterative bronchiolitis is unlikely and there is limited data in the third case for definitive conclusions concerning causality.

No event was reported more than once in pediatric patients receiving nelfinavir during the pediatric exclusivity period. There was one pediatric death from respiratory distress due to obliterative bronchiolitis in a premature infant at 60 weeks of age that was unlikely related to the use of nelfinavir.

This review does not reveal any new safety concerns for the use of nelfinavir in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

2 PRODUCTS, INDICATIONS, PEDIATRIC FILING HISTORY, AND PEDIATRIC LABELING

Viracept® (nelfinavir) is a protease inhibitor indicated in combination with other antiretroviral agents for the treatment of the human immunodeficiency virus (HIV) infection. The two available tablets contain 250 mg nelfinavir mesylate and 625 mg nelfinavir mesylate, respectively; the oral powder contains 50 mg of nelfinavir as the free base in each level scoopful (1 gram).

The 250 mg tablet and the oral powder were approved March 14, 1997. The **Pediatric Use** subsection under **PRECAUTIONS** in the original March 1997 Viracept® label indicated that the safety and effectiveness of Viracept have been established in patients from 2 to 13 years of age at a dose of 20-30 mg/kg/dose given three times daily and not to exceed 750mg three times daily. The adverse events profile in pediatric patients was similar to that seen in adults and there were no studies in patient less than 2 years of age.

In November 1999, a twice-daily dosing regimen was approved in adults but was not studied in pediatric patients. In May 2000, nelfinavir received traditional approval; no changes to the **Pediatric Use** Section were implemented except to add that studies in children less than 2 years of age were ongoing. The 625 mg tablet strength was approved in April 2004 with no changes to the **Pediatric Use** section of the labeling.

The most recent approval (March 2004) in response to the Pediatric Written Request significantly changed the **Pediatric Use** section of the label. Twice daily dosing recommends, additional safety data, and a statement concerning the effective dosing of nelfinavir in children less than 2 years of age were added (see Appendix).

3 AERS SEARCH RESULTS: NELFINAVIR

The AERS search included all sources – U.S. and foreign.

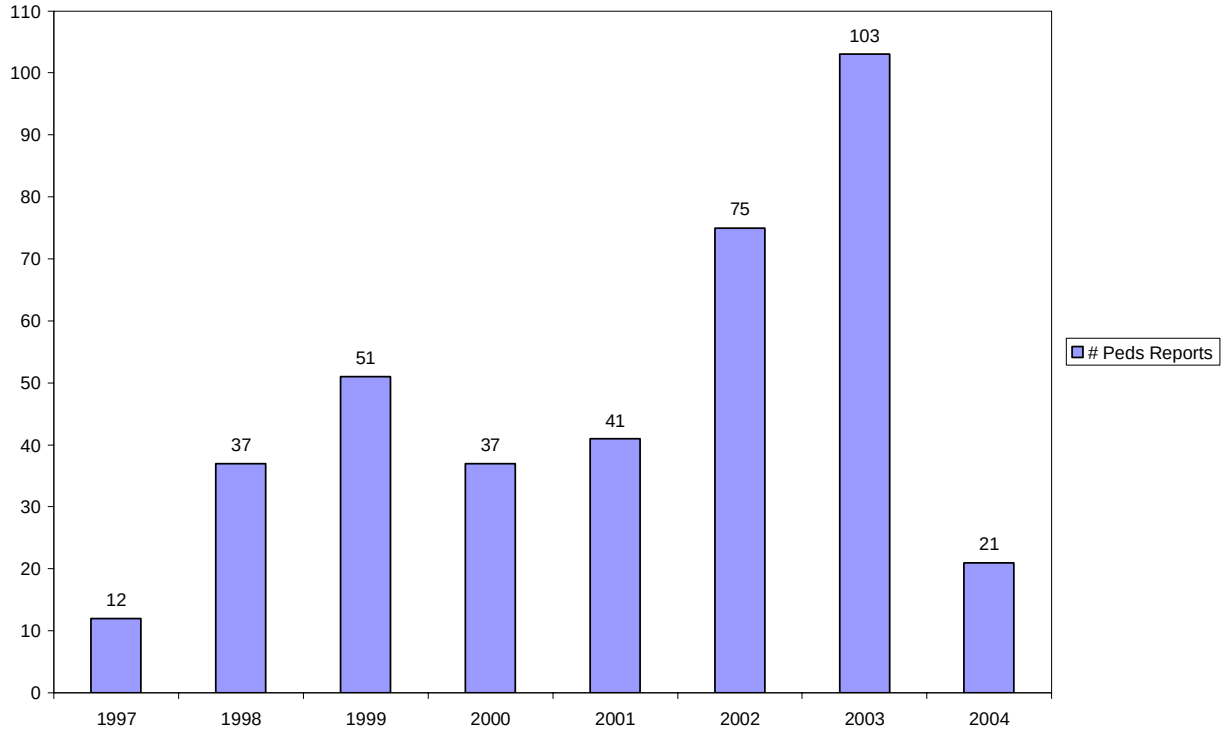
3.1 Total reports in AERS from marketing approval date (03/14/1997) through data cut-off date (10/04/2004).

3.1.1 Raw counts of reports: see Table 1.

Table 1: Raw counts* of total nelfinavir reports in AERS from marketing approval date through data cut-off date (10/4/04)			
	All reports (US)	Serious** (US)	Death (US)
All ages***	3344 (1319)	3207(1258)	417(205)
Adults (17+)	2353 (857)	2243(810)	274(98)
Peds (0-16)	377 (149)	374(146)	19(8)
*May include duplicates **Serious outcomes include outcome "Other" ***Includes null ages			

Reporting trend for pediatric reports from approval date (3/1997)

Figure 1 Reporting Trend for Pediatric Reports from Approval Date (3/1997)



3.1.2 Counts of the top 20 reported events as preferred terms since approval for all ages (including null ages), adults, and pediatric age groups; see Table 2, 3 and 4. *Italicized* events were among the most frequently reported events in pediatric patients, but not in adults; underlining signifies the event is not included in the current labeling[1].

Table 2: Counts of top 20 reported events (preferred terms) since approval*		
	Top 20 preferred terms	**Count**
All ages (including null ages)	Complications of maternal exposure to therapeutic drugs	380
	Maternal drugs affecting fetus	299
	Hypertriglyceridemia	231
	Diarrhea	228
	Pyrexia	221
	Cesarean section	217
	Vomiting	205
	Blood lactic acid increased	177
	Neonatal disorder	170
	Pregnancy	151
	Lactic acidosis	148
	Anemia	135
	Abdominal pain	133
	Blood creatine phosphokinase increased	129
	Myocardial infarction	128
	Asthenia	126
	Nausea	126
	Dermatitis	124
	Premature baby	119
	Condition aggravated	112
* Raw counts: includes terms from duplicate reports		

[1] Some of the "unlabeled" events may be adequately covered by terms listed in the labeling. For example, fatigue per se is not labeled but asthenia is a labeled event.

Table 3: Counts of top 20 reported events (preferred terms) since approval*		
	Top 20 preferred terms	**Count**
Adults (17+ years)	Pyrexia	199
	Diarrhea	186
	Vomiting	178
	Complications of maternal exposure to therapeutic drugs	149
	Myocardial infarction	122
	Lactic acidosis	118
	Nausea	117
	Abdominal pain	113
	Asthenia	113
	Condition aggravated	98
	Dyspnea	88
	Arthralgia	86
	Weight decreased	85
	Dermatitis	82
	Pregnancy	82
	Hypertriglyceridemia	81
	Anemia	78
	Headache	78
	Liver Function tests abnormal	77
	Hyperglycemia	75
* Raw counts: includes terms from duplicate reports		

Table 4: Counts of top 20 reported events (preferred terms) since approval*		
	Top 20 preferred terms	**Count**
Pediatrics (0-16 years)	*Maternal drugs affecting fetus*	158
	Complications of maternal exposure to therapeutic drugs	126
	Neonatal disorder	117
	Cesarean section	109
	Hypertriglyceridemia	95
	Blood lactic acid increased	92
	Neutropenia neonatal	77
	Premature baby	60
	Blood creatine phosphokinase increased	53
	Anemia neonatal	50
	Anemia macrocytic	41
	Pregnancy	37
	Blood ketone body increased	35
	Lactate pyruvate ration increased	34
	Macrocytosis	33
	Anemia	31
	Gastroesophageal reflux disease	29
	Platelet count increased	29
	AbdominaldDistention	28
	Neutropenia	28
* Raw counts: includes terms from duplicate reports		

3.2 Total reports in AERS from Pediatric Exclusivity approval date (9/4/2003) through AERS data cut-off date (10/4/2004):

3.2.1 Raw counts of reports: see Table 5.

Table 5: Raw counts* of reports from pediatric exclusivity approval date through AERS data cut-off date			
	All reports (US)	Serious** (US)	Death (US)
All ages***	269 (70)	264(67)	33 (4)
Adults (17+)	182 (44)	177 (41)	19 (2)
Peds (0-16)	30 (9)	30 (9)	2 (0)
*May include duplicates **Serious outcomes include outcome "Other" ***Includes null ages			

3.2.2 Counts of top 20 reported events as preferred terms in the pediatric exclusivity period for all ages (including null ages), adults, and pediatric age groups; see Table 6. *Italicized* events were among the most frequently reported events in pediatric patients, but not in adults; underlining signifies the event is not included in the current labeling[2].

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity approval date*		
	Top 20 preferred terms	**Count**
All ages (including null ages)	Drug exposure during pregnancy	41
	Maternal drugs affecting fetus	36
	Premature baby	28
	Cesarean section	27
	Diarrhea	22
	Pregnancy	22
	Aspartate aminotransferase increased	19
	Complication of maternal exposure to therapeutic drugs	17
	Hypertriglyceridemia	17
	Neonatal disorder	17
	Vomiting	16
	Alanine aminotransferase increased	15
	Lactic acidosis	14
	Nausea	13
	Anemia	12
	Hyperlactacidemia	12
	Anorexia	11
	Asthenia	11
	Blood lactic acid increased	11
	Pyrexia	11

[2]Some of the "unlabeled" events may be adequately covered by terms listed in the labeling. For example, fatigue per se is not labeled but asthenia is a labeled event.

Table 6: Counts of top 20 reported events (preferred terms) from pediatric exclusivity approval date*		
	Top 20 preferred terms	**Count**
Adults (17+ years)	Diarrhea	19
	Vomiting	15
	Nausea	13
	Aspartate aminotransferase increased	12
	Lactic acidosis	12
	Anorexia	11
	Complication of maternal exposure to therapeutic drugs	11
	Pyrexia	11
	Alanine aminotransferase increased	10
	Asthenia	10
	Pregnancy	10
	Drug exposure during pregnancy	9
	Gamma-glutamyltransferase increased	9
	Hypertriglyceridemia	9
	Anemia	8
	Arthralgia	8
	Blood alkaline phosphatase increased	8
	Cesarean section	8
	Cytolytic hepatitis	8
	Osteonecrosis	8
	Weight decreased	8
Pediatric patients (0-16 years)	*Maternal drugs affecting fetus*	15
	Premature baby	13
	Cesarean section	12
	Drug exposure during pregnancy	11
	Neonatal disorder	9
	Pregnancy	6
	Blood lactic acid increased	5
	Blood lactate dehydrogenase increased	4
	Gastroesophageal reflux disease	4
	Hypertriglyceridemia	4
	Patent ductus arteriosus	4
	Abdominal distension	3
	Aspartate aminotransferase increased	3
	Cerebellar syndrome	3
	Complication of maternal exposure to therapeutic drugs	3
	Convulsions neonatal	3
	Extrapyramidal disorder	3
	Macrocytosis	3
	Neonatal respiratory distress syndrome	3
	Neutropenia neonatal	3
	Platelet count decreased	3
* Raw counts: includes terms from duplicate reports		

4 POSTMARKETING HANDS-ON REVIEW OF ALL PEDIATRIC ADVERSE EVENT REPORTS FROM ALL SOURCES RECEIVED DURING THE 1-YEAR PERIOD AFTER PEDIATRIC MARKET EXCLUSIVITY WAS GRANTED

A. Description of demographic characteristics of 3 pediatric cases regarding gender, age, indications, doses, and outcomes: see Table 7. (The 24 cases in infants following maternal exposure to nelfinavir are not included in this table.)

Table 7: Characteristics of pediatric cases reported during the 1-year period after receiving pediatric market exclusivity		
Gender	Female: 0 Male: 2 Unknown: 1	
Age (Standard AERS age breakdown)	0-<1 mo: 0 1 mo- <2 yrs: 2 2-5 yrs: 0 6-11 yrs: 0 12-16 yrs: 1	
Daily dose	1225 mg twice daily: Not stated:	1(14 year old) 2
Indications	Treatment of HIV infection:	3
Serious outcomes	Death (DE): Assessed as medically serious by reporter (OT):	1 2

B. Labeling status of the frequently reported adverse events and similarities to adult adverse event profile; pediatric deaths during the pediatric exclusivity period.

There are 11 events reported in the 3 unduplicated pediatric cases: **attention deficit/hyperactivity disorder-1 and psychomotor hyperactivity-1; arthritis-1, bronchiolitis-1, central venous catherisation-1, obliterative bronchiolitis-1, premature baby-1, and respiratory distess-1; liver function tests abnormal-1, muscular weakness, and renal tubular acidosis.**

No event was reported more than one time in pediatric patients during the pediatric exclusivity period. None of the pediatric events except for abnormal liver function tests were among the most frequently reported events for adults, either during the pediatric exclusivity period or for the entire marketing life of nelfinavir. In addition, very few of the pediatric events are labeled events for nelfinavir. However, with only one case reported for any given event, it would be premature to recommend any changes to the nelfinavir labeling or to conclude that the pediatric safety profile is different from that for adults.

One pediatric patient died from obliterative bronchiolitis but the death was considered unlikely related to the use of nelfinavir. No other pediatric patients were hospitalized and no other events were characterized as life threatening during the pediatric exclusivity period.

C. Summary of pediatric adverse event profile during pediatric exclusivity period.

We received 3 unduplicated, non-excluded cases for pediatric patients receiving nelfinavir during the pediatric exclusivity period, reporting 11 events. Table 6 lists the top 20 preferred terms (PTs) reported in pediatric patients during the pediatric exclusivity period with the vast majority of the events reported in infants following maternal fetal exposure to nelfinavir.

The 11 events in the 3 unduplicated pediatric cases are not all listed in Table 6 but are as follows: **attention deficit/hyperactivity disorder-1 and psychomotor hyperactivity-1; arthritis-1, bronchiolitis-1, central venous catherisation-1, obliterative bronchiolitis-1, premature baby-1, and respiratory distess-1; liver function tests abnormal-1, muscular weakness, and renal tubular acidosis**. Except for abnormal liver function tests and arthritis, all of the events reported for the 3 pediatric patients during the pediatric exclusivity period are unlabeled for nelfinavir.

Attention deficit/hyperactivity and psychomotor hyperactivity (Case# 3991725)
A 14 year old HIV-positive Afro-Caribbean male receiving antiretroviral therapy including nelfinavir 1225mg twice daily, didanosine 200mg daily, and stavudine 20mg twice daily developed a mild behavioral disturbance. Attention-deficit hyperactivity disorder (ADHD) "was considered" but thought unlikely by the reported. This is an otherwise poorly documented report.

Hyperactivity is not a labeled event for nelfinavir; however anxiety and hyperkinesias are listed in the **ADVERSE REACTIONS** section under nervous system. With only one case reported, it would be premature to recommend any changes to the nelfinavir labeling.

Neuromuscular weakness syndrome (Case# 4166154)
This case is included in a literature review of patients experiencing neuromuscular weakness syndrome while taking antiretrovirals[3]. This report describes a one year old male that experienced medically serious neuromuscular weakness syndrome, elevated liver function tests, and renal tubular acidosis while taking didanosine, zidovudine and nelfinavir. Lactate level was 7.11 mmol/L and neurological findings showed profound motor delay and areflexia. Histological findings revealed generalized atrophy and muscle fiber size variation, sarcomeric disarray and myofibril loss, and mitochondrial abnormalities with normalization after antiretroviral (ARV) drug discontinuation. The authors concluded that a severe neuromuscular weakness syndrome may occur in HIV-infected individuals. The association with hyperlactatemia and nucleoside reverse transcriptase inhibitor (NRTI) exposure supports mitochondrial toxicity as a pathogenesis.

Myalgia, myasthenia, and myopathy are listed in the **ADVERSE REACTIONS** section of the nelfinavir label under musculoskeletal system.

[3] Simpson D, Estanislao L, Evans S, McArthur J, Marcus K, Truffa M, et al. HIV-associated Neuromuscular Weakness. AIDS 2004; 18(10): 1403-12.

Obliterative bronchiolitis, arthritis and respiratory distress (Case# 4156597)
A report in the literature[4] describes a 60 week old infant that was hospitalized with the suspicion of arthritis experienced bronchiolitis and expired while participating in a stavudine, didanosine and nelfinavir open-label study. The infant's mother was HIV positive and delivered an HIV positive premature infant at 30 weeks of gestation. Antiretroviral therapy consisting of stavudine, didanosine and nelfinavir was initiated 15 weeks after birth. The infant was hospitalized twice for central line placement and suspicion of arthritis, and also experienced two episodes of bronchiolitis. The infant died at 60 weeks of age, from respiratory distress due to obliterant bronchiolitis related to prematurity and not related to HIV infection.

Other: Maternal to Fetal Exposure (N=24)
In addition to the 3 pediatric cases there are 24 reports in infants following transplacental exposure to nelfinavir (see attachment 2). A review of these cases did not reveal any particular patterns of toxicity with regard to the use of nelfinavir. Eight of the infants were considered premature having been born at less than 38 weeks of gestation. All 24 of the infants were exposed to multiple antiretroviral agents with drug exposure occurring during various weeks of gestational development.

The following events were reported more than once (raw counts may include duplicates): *premature baby-13, caesarian section-12, neonatal disorder-9, blood lactic acid increased-5, blood lactate dehydrogenase increased-4, GERD-4, hypertriglyceridenia-4, patent ductus arteriosus-4, abdominal disention-3, AST increased-3, macrocytosis-3, neonatal respiratory distress syndrome-3, neutropenia neonata-3, platelet count decreased-3, ALT increased-2, anemia-2, anemia neonatal-2, apgar score low-2, blood creatinine increased-2, constipation-2, developmental delay-2, diarrhea-2, fetal growth retardation-2, grand mal convulsion-2, hypertonia-2, lactate pyruvate ration increased-2, mastitis-2, platelet count increased-2, rhinitis-2, and Trisomy 21-2.*

5 SUMMARY

The AERS database was searched for reports of adverse events occurring with the use of nelfinavir in pediatric patients. We focused on the 1-year period following the approval of pediatric exclusivity, 9/4/2003 to 9/4/2004. The profile of the adverse events preferred terms was compared to the adverse event profile for adult patients and to the product labeling.

We reviewed 3 unduplicated, non-excluded pediatric cases reported to the FDA during the pediatric exclusivity period. No events were reported more than one time in pediatric patients receiving nelfinavir during the pediatric exclusivity period. One pediatric patient died from obliterative bronchiolitis but the death was considered unlikely related to the use of nelfinavir. No other pediatric patients were hospitalized and no other events were characterized as life threatening during the pediatric exclusivity period.

[4] Aboulker JP, Babiker A, Chaix ML, Compagnucci A, Darbyshire J, et al. Highly Active Antiretroviral Therapy Started in Infancts under 3 Months of Age: 72 Week Follow-up for CD4 Cell Count, Viral Load, and Drug Resistance Outcomes. AIDS 2004; 18(2):237-45.

This review does not reveal any new safety concerns for the use of nelfinavir in pediatric patients. We will continue routine monitoring of adverse events in pediatric patients.

/s/ Melissa M. Truffa 12-10-04
Melissa M. Truffa, R.Ph.

Concur:

/s/ Mark Avigan 12-15-2004
Mark Avigan, M.D., C..M..

Appendix

Drug Product Information

The labeling for Viracept® can be accessed at Drugs @ FDA
http://www.fda.gov/cder/foi/label/2004/20778slr003,20779slr044,21503slr003_viracept_lbl.pdf

The Viracept® labeling contains information regarding pediatric use in the following sections:

CLINICAL PHARMACOLOGY
Special Populations
Pediatrics: The pharmacokinetics of nelfinavir have been investigated in 5 studies in pediatric patients from birth to 13 years of age either receiving VIRACEPT three times or twice daily. The dosing regimens and associated AUC_{24} values are summarized in Table 3.

Table 3
Summary of Steady-state AUC_{24} of Nelfinavir in Pediatric Studies

Protocol No.	Dosing Regimen[1]	N[2]	Age (years)	AUC_{24} (mg.hr/L) Arithmetic mean ± SD
AG1343-524	20 (19-28) mg/kg TID	14	2-13 years	56.1± 29.8
PACTG 725	55 (48-60) mg/kg BID	6	3-11 years	101.8± 56.1
PENTA 7	40 (34-43) mg/kg TID	4	2-9 months	33.8± 8.9
PENTA 7	75 (55-83) mg/kg BID	12	2-9 months	37.2± 19.2
PACTG 353	40 (14-56) mg/kg BID	10	6 weeks	44.1± 27.4
			1 week	45.8± 32.1

[1] Protocol specified dose (actual dose range)
[2] N: number of subject with valuable pharmacokinetic results
C_{trough} values are not presented in the table because they are not available for all studies

Pharmacokinetic data are also available for 86 patients (age 2 to 12 years) who received VIRACEPT 25-35 mg/kg TID in Study AG1343-556. The pharmacokinetic data from Study AG1343-556 were more variable than data from other studies conducted in the pediatric population; the 95% confidence interval for AUC_{24} was 9 to 121 mg.hr/L.

Overall, use of VIRACEPT in the pediatric population is associated with highly variable drug exposure. The high variability may be due to inconsistent food intake in pediatric patients. (see PRECAUTIONS Pediatric USE; DOSAGE AND ADMINISTRATION).

PRECAUTIONS
Pediatric Use
The safety and effectiveness of VIRACEPT have been established in patients from 2 to

13 years of age. The use of VIRACEPT in these age groups is supported by evidence from adequate and well-controlled studies of VIRACEPT in adults and pharmacokinetic studies and studies supporting activity in pediatric patients. In patients less than 2 years of age, VIRACEPT was found to be safe at the doses studied but a reliably effective dose could not be established (see CLINICAL PHARMACOLOGY: Special Populations, ADVERSE REACTIONS: Pediatric Population, and DOSAGE AND ADMINISTRATION: Pediatric Patients).

The following issues should be considered when initiating VIRACEPT in pediatric patients:

- In pediatric patients ≥ 2 years of age receiving VIRACEPT as part of triple combination antiretroviral therapy in randomized studies, the proportion of patients achieving an HIV RNA level <400 copies/mL through 48 weeks ranged from 26% to 42%.
- Response rates in children <2 years of age appeared to be poorer than those in patients ≥ 2 years of age in some studies.
- Highly variable drug exposure remains a significant problem in the use of VIRACEPT in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing. Pharmacokinetic results from the pediatric studies are reported in Table 3 (see Clinical Pharmacology, Special Populations).

Study 556 was a randomized, double-blind, placebo-controlled trial with VIRACEPT or placebo coadministered with ZDV and ddI in 141 HIV-positive children who had received minimal antiretroviral therapy. The mean age of the children was 3.9 years. 94 (67%) children were between 2 - 12 years, and 47 (33%) were < 2 years of age. The mean baseline HIV RNA value was 5.0 log for all patients and the mean CD4 cell count was 886 cells/mm^3 for all patients. The efficacy of VIRACEPT measured by HIV RNA <400 at 48 weeks in children. 2 years of age was 26% compared to 2% of placebo patients (p= 0.0008). In the children < 2 years of age, only 1 of 27 and 2 out of 20 maintained an undetectable HIV RNA level at 48 weeks for placebo and VIRACEPT patients respectively.

PACTG 377 was an open-label study that randomized 181 HIV treatment-experienced pediatric patients to receive: d4T+NVP+RTV, d4T+3TC+NFV, d4T+NVP+NFV, or d4T+3TC+NVP+NFV with NFV given on a TID schedule. The median age was 5.9 28 years and 46% were male. At baseline the median HIV RNA was 4.4 log and median CD4 cell count was 690 cells/mm^3. Sub-study PACTG 725 evaluated d4T+3TC+NFV with NFV given on a BID schedule. The proportion of patients with detectable viral load at baseline achieving HIV RNA <400 copies/mL at 48 weeks was: 41% for d4T+NVP+RTV, 42% for d4T+3TC+NFV, 30% for d4T+NVP+NFV, and 52% for d4T+3TC+NVP+NFV. No significant clinical differences were identified between patients receiving VIRACEPT in BID or TID schedules.

VIRACEPT has been evaluated in 2 studies of young infants. The PENTA 7 study was an open-label study to evaluate the toxicity, tolerability, pharmacokinetics, and activity of NFV+d4T+ddI in 20 HIV-infected infants less than 12 weeks of age. PACTG 353 evaluated the pharmacokinetics and safety of VIRACEPT in infants born to HIV-infected women receiving NFV as part of combination therapy during pregnancy.

ADVERSE REACTIONS

Pediatric Population

VIRACEPT has been studied in approximately 400 pediatric patients in clinical trials from birth to 13 years of age. The adverse event profile seen during pediatric clinical trials was similar to that for adults.

The most commonly reported drug-related, treatment-emergent adverse events reported in the pediatric studies included: diarrhea, leukopenia/neutropenia, rash, anorexia, and abdominal pain. Diarrhea, regardless of assigned relationship to study drug, was reported in 39% to 47% of pediatric patients receiving VIRACEPT in 2 of the larger treatment trials. Leukopenia/neutropenia was the laboratory abnormality most commonly reported as a significant event across the pediatric studies.

DOSAGE AND ADMINISTRATION

Pediatric Patients (2-13 years): In children 2 years of age and older, the recommended oral dose of VIRACEPT oral powder or 250 mg tablets is 45 to 55 mg/kg twice daily or 25 to 35 mg/kg three times daily. All doses should be taken **with a meal**. Doses higher than the adult maximum dose of 2500 mg per day have not been studied in children. For children unable to take tablets, VIRACEPT Oral Powder may be administered. The oral powder may be mixed with a small amount of water, milk, formula, soy formula, soy milk or dietary supplements; once mixed, the entire contents must be consumed in order to obtain the full dose. If the mixture is not consumed immediately, it must be stored under refrigeration, but storage must not exceed 6 hours. Acidic food or juice (e.g., orange juice, apple juice or apple sauce) are not recommended to be used in combination with VIRACEPT, because the combination may result in a bitter taste. VIRACEPT Oral

Powder should not be reconstituted with water in its original container. The healthcare provider should assess appropriate formulation and dosage for each patient. Crushed 250 mg tablets can be used in lieu of powder. Tables 12 and 13 provide dosing guidelines for VIRACEPT tablets and powder based on age and body weight.

Table 12

Dosing Table for Children ≥ 2 years of age (tablets)

Body Weight		**Twice Daily (BID) 45-55 mg/kg ≥ 2 years**	**Three times Daily (TID) 25-55 mg/kg ≥ 2 years**
Kg.	**Lbs.**	# of tablets (250 mg)	# of tablets (250 mg)
10 - 12	**22 - 26.4**	2	1
13 - 18	**28.6 – 39.6**	3	2
19 - 20	**41.8 - 44**	4	2
≥21	**≥46.2**	4-5[1]	3[2]

[1] For BID dosing, the maximum dose per day is 5 tablets BID

[2] For TID dosing, the maximum dose per day is 3 tablets TID

Table 13
Dosing Table for Children ≥ 2 years of age (powder)

Body Weight		**Twice Daily (BID) 45-55 mg/kg ≥ 2 years**		**Three times Daily (TID) 25-55 mg/kg ≥ 2 years**	
Kg.	Lbs.	Scoops of Powder (50mg/l g)	Teaspoons[1] of Powder	Scoops of Powder (50mg/l g)	Teaspoons[1] of Powder
9.0 to< 10.5	20 to < 23	10	2 ½	6	1 ½
10.5 to < 12	23 to < 26.5	11	2 3/4	7	1 ¾
12 to < 14	26.5 to < 31	13	3 1/4	8	2
14 to < 16	31 to < 35	15	3 ¾	9	2 ¼
16 to < 18	35 to < 39.5	Not recommneded[2]	Not recommneded[2]	10	2 ½
18 to < 23	39.5 to < 50.5	Not recommneded[2]	Not recommneded[2]	12	3
23≥	≥ 50.5	Not recommneded[2]	Not recommneded[2]	15	3 ¾

[1] If a teaspoon is used to measure Viracept oral powder, 1 level teaspoon contains 200 mg of Viracept (4 level scoops equal 1 level teaspoon).

[2] Use Viracept 250 mg tablets

Additionally, the **PRECAUTIONS** section gives information on use of Viracept during pregnancy:

Pregnancy - Pregnancy Category B
There were no effects on fetal development or maternal toxicity when nelfinavir was administered to pregnant rats at systemic exposures (AUC) comparable to human exposure. Administration of nelfinavir to pregnant rabbits resulted in no fetal development effects up to a dose at which a slight decrease in maternal body weight was observed; however, even at the highest dose evaluated, systemic exposure in rabbits was significantly lower than human exposure. Additional studies in rats indicated that exposure to nelfinavir in females from mid-pregnancy through lactation had no effect on the survival, growth, and development of the offspring to weaning. Subsequent reproductive performance of these offspring was also not affected by maternal exposure to nelfinavir. However, there are no adequate and well-controlled studies in pregnant women taking VIRACEPT. Because animal reproduction studies are not always predictive of human response, VIRACEPT should be used during pregnancy only if clearly needed.

Limitations of the Adverse Event Reporting System (AERS)
AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or be used for comparing risk between products.

Attachment 1

Table 8—Line Listing of All Pediatric Cases Received During the Pediatric Exclusivity Period (N=3)										
AERS Case #	**Year received**	**Report type**	**AGE**	**SEX**	**US or non-US**	**Outcome**	**ARV Therapy**	**Nelfinavir Dose** **Time to onset (days)**	**All reaction terms reported**	**Comments**
4166154	2004	Expedited (15-day)	1 year	Male	US	OT	Nelfinavir Zidovudine Stavudine	Unk	Neuromuscular weakness, LFTs abnormal, Renal tubular acidosis	Literature Report: HIV-associated neuromuscular weakness syndrome, AIDS 2004 Hyperlactatemia and nucleoside exposure support mitochondrial toxicity as pathogenesis.
4156597	2004	Expedited (15-day)	14 months	Unk	Non-US	DE HO	Nelfinavir Stavudine Didanosine	Unk	Arthritis, Obliterative bronchiolitis, premature baby, respiratory distress	HIV (+) 30-week premature baby Two prior episodes of bronchiolitis. Patient died at 60 weeks due to obliterative bronchiolitis due to prematurity. Literature report: HAART started in infants under 3 months of age: 72 week follow-up for CD4 cell count, viral load and drug resistance, AIDS 2004
3991725	2003	Expedited (15-Day)	14 years	Male	Non-US	OT	Nelfinavir Stavudine Didanosine	1225mg BID	Attention deficit, Hyperactivity disorder	ADHD considered but thought unlikely by reporter. Event not resolved at time of report

Attachment 2

Table 8—All Maternal to Fetal Exposure Cases Received During the Pediatric Exclusivity Period (N=24)					
	Case #	**Sex/age/ location**	**Antiretrovirals**	**Infant's Reported Adverse Event**	**Comment**
1.	4008318	M/newborn (b)(6)	Mother: ddI/NVP/ZDV week 0-14 of gestation NFV/SQV/ABC/3TC started at 14 weeks of gestation	Patent ductus arteriosus (PDA)	31 year old female prematurely delivered triplets at 29 weeks of gestation. Triplet "C" was diagnosed with patent ductus arteriosus (PDA) that resolved before hospital discharge. Mother CD4 count < 200.
2.	4008687	F/newborn (b)(6)	Mother: NFV/ 3TC/ZDV started at 14 weeks of gestation At delivery: zidovudine IV	Hyaline membrane disease, respiratory distress, patent ductus arteriosus, pneumothorax, persistent pulmonary hypertension of newborn (PPHN)	Female infant born by C- section at 39 weeks of gestation to 35 year old mother. Admitted to NICU with hyaline membrane disease and respiratory distress. Patient given Surfactant x 3 doses. Also diagnosed with pneumothorax and PPHN. Patient discharged 15 days after birth in good condition and on ZDV prophylactic therapy 6mg q6h.
3.	4009614	M/newborn (b)(6)	Mother: NFV/3TC/ZDV	Respiratory disorder	Premature labor at 34 weeks of gestation requiring an emergency caesarean section. Baby developed a respiratory disorder some time after birth and is reported to have fully recovered.
4.	3999544	F/newborn (b)(6)	Mother: NFV/d4T/ddI/3TC/ZDV received NFV during 1st and 3rd trimester Baby: ZDV syrup after birth	Abdominal distention, feeding problem, anemia	Born at 38 weeks of gestation. Abdominal distention, regurgitation, feeding problems, and anemia occurred after ZDV syrup was started. The baby has recovered.
5.	4014983	F/newborn (b)(6)	Mother: NFV/3TC/ZDV until 9 weeks of gestation. Then ddI/d4T/EFV from 35 weeks. At delivery: zidovudine IV	Neutropenia, angioma, hypertriglyceridemia, gastroesophageal reflux	Baby born with neutropenia and an angioma on the back of the neck. Infant received a single dose of nevirapine at birth and stavudine for 6 weeks. Mother received salbutamol and Spasfon during entire pregnancy

Table of All Maternal to Fetal Exposure Cases Received During the Pediatric Exclusivity Period (N=24)					
	Case #	**Sex/age/ location**	**Antiretrovirals**	**Infant's Reported Adverse Event**	**Comment**
6.	4036452	M/newborn/ (b)(6)	Mother: NFV/3TC/ZDV x 3 months during 3rd trimester. NVP x 1 mon in 2nd trimester, at delivery zidovudine IV	Trisomy 21	Baby born at 34 5/7 weeks gestation with Downs Syndrome. Mother is 44 year old Black women.
7.	4032442	M/newborn/ (b)(6)	Mother: NFV/ddI/ZDV throughout pregnancy	Patent ductus arteriosus, Trisomy 21	31-year-old female delivered a Hispanic male infant at 38 weeks gestation.
8.	3717245	[illegible]wborn/ (b)(6)	NFV/ddI/d4T throughout pregnancy, at delivery: zidovudine IV	Neutropenia, increased transaminases, lactacidemia, Abdominal distention	Born 38.5 weeks gestation. Infant received 6 weeks of therapy with stavudine. 18 moth follow-up clinical and neurological assessment normal. Increased transaminases and neutropenia still present at 18 months
9.	3748418	Unk/newborn (b)(6)	NFV/ZDV/3TC/ddI	Decreased pyruvate (at 1 month), glaucoma (at 3 months), increased amylase and lactic acid (at 6 months)	At 2.5 years biologically normal, glaucoma still present, delayed motor and mental development. Recklinghausen disease ruled out.
10.	3827383	M/newborn (b)(6)	NFV/ddI/d4T from 28 wks gestation	Lactacidemia, hypertriglyceridemia	Born 38.5 weeks of gestation. Infant received stavudine and Didanosine for 6 weeks. At 3.5 years mental retardation and speech disorder.
11.	4060677	[illegible]born (b)(6)	NFV/ZDV/3TC started 3 weeks prior to delivery, at delivery: zidovudine IV	Anemia Sudden death	Normal full term infant with anemia. Infant received oral zidovudine x 1 day. Sudden death one day after birth. Autopsy= asphyxia, otherwise normal except anemia. Suspected infanticide
12.	4196946	M/newborn (b)(6)	NFV/ZDV/3TC from 30 weeks of gestation	Gastroesophageal reflux disease (1st month), increased LDH (at 2 months)	Normal infant born at 39 weeks gestation, recived oral zidovudine for 6 weeks. At 4 months abnormal MRI. At 14 months of age motor dysfunction of left leg and arm.
13.	4208299	[illegible]born (b)(6)	NFV/ZDV/3TC throughout pregnancy	Testicular atrophy (at 6 months of age)	Normal infant at birth
14.	3721100	(b)(6)	IDV/ddI/d4T until 4th wk gestation then NFV/ddI/d4T from 22 wks gestation, at delivery: zidovudine IV	Neutropenia, macrocytosis, abdominal distention, decreased platelets, constipation, blood lactate increased, hypertriglyceridemia, mastitis, increased pyruvate, ketosis	Infant received 6 weeks of therapy with stavudine. At 12 and 18 months grade I neutropenia.

Table of All Maternal to Fetal Exposure Cases Received During the Pediatric Exclusivity Period (N=24)					
	Case #	**Sex/age/ location**	**Antiretrovirals**	**Infant's Reported Adverse Event**	**Comment**
15.	4099973	Unk/newborn	NFV/ZDV/3TC	Congenital anomaly	Limited data on ARV therapy and congenital anomaly
16.	4122455	[redacted]	NFV/NVP until 22 wk gestation, ZDV/3TC throughout pregnancy, and LPV/RTV/TDF from 22 wks gestation	Congenital lung malformation, premature baby	Born at 35 weeks gestation. Congenital cystic adenoid malformation of the right lung at 3.5 months was diagnosed.
17.	4138634	F/newborn	NFV/ZDV/3TC throughout pregnancy	Premature baby, hepatomegaly, increased LDH lactic acid, leukopenia, pulmonary hypertension, cardiomegaly, foramen ovale patent, hyaline membrane disease, decreased platelets	Premature baby born at 29 weeks of gestation. Infant treated with oral zidovudine, Curosurf (phospholipidfractiona, porcine lung, NaCl), Calcium folate, Vitamin K, nitrate caffeine, Pulmicort, and posicycline.
18.	4141052	M/newborn	NFV/ZDV/3TC started in 3rd trimester of pregnancy, at delivery zidovudine IV	Glucose-6-phosphate dehydrogenase deficiency	Born at 39 weeks of gestation. Glucose-6-phosphate dehydrogenase deficiency confirmed at 6 months.
19.	4162568	F/newborn	NFV/ABC/NVP throughout pregnancy	Anemia and neutropenia (at birth)	Born at 39 weeks of gestation. Infant received oral zidovudine for 6 weeks. At 30 months of age patient developed malignant cerebral tumor and was diagnosed with an ependymoma
20.	4163308	F/newborn	NFV/ZDV/3TC from 18 weeks of gestation, at delivery IV zidovudine	Patent ductus arteriosus Ventricular septal defect	Born at 38 weeks of gestation to a 19 year mother. Mother with condyloma and vulvovaginitis in 2nd trimester.
21.	4022267 4168865 4168866	[redacted]	NFV/ZDV/3TC during 2nd and 3rd trimesters	Premature baby, convulsions, cerebellar syndrome, extrapyramidal syndrome, axonal neuropathy	Ethambutol and isoniaziade and rifampicinel for TB during 2nd and 3rd trimester. Tetraplegia from toxplasmosis lesion during pregnancy treated with corticosteroids, sulfadiazine and pyrimethamine during 3rd trimester. Premature male infant born at 33 weeks of gestation by C-section. Infant received zidovudine, phenytoin and phenobarbital
22.	4195885 4208906	M/newborn	NFV/Kaletra/ZDV/3TC Delivery IV zidovudine	Premature baby, acute respiratory distress	Born prematurely at 29 weeks of gestation by emergency C-section. Mother with toxemia of pregnancy

Table of All Maternal to Fetal Exposure Cases Received During the Pediatric Exclusivity Period (N=24)					
	Case #	**Sex/age/ location**	**Antiretrovirals**	**Infant's Reported Adverse Event**	**Comment**
23.	4215870	M/newborn (b)(6)	EFV/3TC/ZDV at conception EFV changed to NFV throughout pregnancy, Delivery IV zidovudine	Premature baby, low birth weight	Born prematurely at 26 weeks of gestation to 31 year old mother
24.	4220708	F/newborn (b)(6)	NFV/ZDV/3TC during 3rd trimester, at delivery IV zidovudine	Anemia, feces pale, macrocytosis, biliary tract disorder, urethral cyst, hemangioma	Normal infant born at 39 weeks of gestation by C-section. Infant received oral zidovudine for 6 weeks.

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/s/

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